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Electrophiles and Acute Toxicity to Fish

by Joop L. M. Hermens*

Effect concentrations in fish LC_{50} tests with directly acting electrophiles are lower than those of unreactive chemicals that act by narcosis. LC_{50} values of more hydrophobic reactive chemicals tend to approach those of unreactive chemicals. Quantitative studies to correlate fish LC_{50} data to physical-chemical properties indicate that LC_{50} values of reactive chemicals depend on hydrophobicity as well as chemical reactivity. In this paper, several examples will be given of chemical structures that are known as direct electrophiles. This classification might be useful to identify chemicals that are more effective at lower concentrations than unreactive compounds. Chemicals that require bioactivation are not included because almost no information is available on the influence of bioactivation on acute toxic effects in aquatic organisms.

Introduction

The toxic effects of electrophiles are based upon their reaction with nucleophilic sites in biological macromolecules, but these cannot be defined in terms of a single mechanism of action. The major effect following an acute exposure to a relatively high dose of an electrophile might be membrane irritancy. More chronic exposure to lower levels might induce cytotoxic effects related to the disturbance of various types of processes within and outside the cell. Many electrophiles have been implicated as genotoxic agents that may act as carcinogens. Several compounds are direct electrophiles, but for many chemicals, electrophiles are formed *in vivo* by metabolic activation (*1*). It comes as no surprise that much attention is directed to possible mutagenic and carcinogenic effects of electrophiles.

Most information on carcinogenicity, toxicity, and bioactivation processes has been derived from mammalian studies or from cellular *in vitro* systems isolated from mammals; much less is known about such processes in fish. It is questionable whether bioactivation is always important in acute toxicity tests with the aquatic species.

LC_{50} concentrations of directly acting electrophiles are generally lower than those of unreactive organic chemicals. In this paper examples will be given of electrophilic chemical structures/moieties that are known to act as direct electrophiles. This classification might be useful in identifying chemicals that are very likely effective at lower concentrations than unreactive compounds.

Intermezzo: Acute LC_{50} Values of Unreactive Organic Chemicals to Fish

Many unreactive organic micropollutants simply act by narcosis in acute toxicity tests with fish. The structural requirements, related to narcosis, are discussed in more detail in the contributions of Veith and Broderius (*2*) and Franks and Lieb (*3*). Two classical QSAR equations are published for the prediction of LC_{50} values in fish: one for the guppy [Eq. (1)] and one for the fathead minnow [Eq. (2)], established by Könemann (*4*) and Veith et al. (*5*), respectively.

$$\log LC_{50}\ (\text{mole/L}) = -0.87 \log K_{ow} - 1.13 \quad (1)$$

$$\log LC_{50}\ (\text{mole/L}) = -0.94 \log K_{ow} + 0.94 \log (0.000068\, K_{ow} + 1) - 1.25 \quad (2)$$

Narcotic effect concentrations for other species and endpoints show similar correlations with K_{ow}. Data for subchronic toxicity to fish and *Daphnia magna* are analyzed by Call et al. (*6*) and Hermens (*7*). Lipnick et al. (*8*) calculated correlations for several endpoints including fish and mammalian LC_{50} values, and Roberts (*9*) published a QSAR equation for upper respiratory tract irritation. The influence of K_{ow} in all these equations simply reflects differences in absorption of the tested compounds.

The structural requirements related to this particular mode of action are rather well defined. Chemicals that act by narcosis include: saturated aliphatic alcohols, saturated ketones, and chlorinated aliphatic (saturated) and aromatic hydrocarbons.

Many pollutants cause lethality at much lower concentrations than predicted by Eqs. (1) or (2) because they act through a specific mode of action or because they may interact directly or indirectly (after bioactivation) with nucleophiles. This paper summarizes those chemical substructures that possess directly reactive properties. The survey is restricted to directly reactive chemicals because little is known of the influence of bioactivation on acute toxic effects. This classification of reactive structures might be useful in identifying

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chemicals that are very likely to be more lethal than unreactive compounds at lower concentrations in acute toxicity experiments.

Chemically Reactive Substructures

Electrophiles can react with several types of nucleophiles. Amino ($-NH_2$), hydroxy (-OH), and sulfhydryl (-SH) groups are the most important of these from a biological point of view because they are found in many biological macromolecules, such as in proteins and in organic bases in DNA. Electrophiles may react with a nucleophilic ligand by different mechanisms of reaction and some of these mechanisms are summarized in Table 1. These mechanisms include nucleophilic displacement reactions (scheme a), addition at a carbon-oxygen bond (scheme b) and addition at a carbon-carbon double bond (scheme c).

Information on directly reactive structures can be drawn from several sources. Many examples of reactive chemicals are given in monographs or review papers on mutagenic and carcinogenic effects of chemicals (*10*). Information on reactive chemicals is also given in literature on organic chemistry (*11,12*), enzyme inhibitors (*13*), alkylation agents (*14*), and sulfhydryl agents (*15*). The -SH group is only one example of a nucleophilic ligand, but it may be a good representative of nucleophiles in general. Organic chemicals that can react with -SH groups are also likely to be reactive towards other nucleophilic ligands such as -OH and $-NH_2$.

The following survey of reactive electrophilic substructures is arranged first according to the atom or chemical group that can bind a nucleophile: acylation reaction, reaction with cyanate, reaction with carbonyl compounds, alkylation and arylation reactions, reaction with metal ions and organometallic compounds, and other miscellaneous reactions with sulfhydryl groups.

Within each of these classes, a division into subclasses can be made according to the specific substructures representing the actual reactive site. The notation of chemical structures shown is hydrogen suppressed unless hydrogen atoms constitute an essential part of the reactive moiety. In addition, the following abbreviations are used: C(ar): aromatic carbon atom; Hal: halogen atom (F, Cl, Br or I); R: H, alkyl group or other arbitrary molecular substructure; C(O) : C=O; $S(O_2)$: O=S=O; P(O) : P=O. Carbon atoms, but also other atoms such as nitrogen, might be substituted with hydrogen or other arbitrary substructures.

Acylation Reactions

In an acylation reaction the end product is an acylated nucleophile such as in a reaction between a sulfhydryl group and acetylchloride in Eq. (3) (*15*).

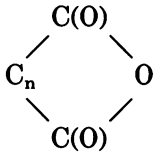
$$R{-}SH + CH_3{-}C(O){-}Cl \rightarrow R{-}S{-}C(O){-}CH_3 + HCl \qquad (3)$$

Examples of chemicals that may react with nucleophiles by acylation (*10,15*) are given below:

ketenes: —C=C=O

acid halides: —C(O)—Hal

carboxylic acid anhydrides:



(n = 2 or 3)

dialkyl carbamoylchloride: $(C_n)_2$—N—C(O)—Cl

Reaction with Isocyanates

Organic isocyanates, as well as isothiocyanates react with an -SH group as depicted in Eq. (4) (*15*):

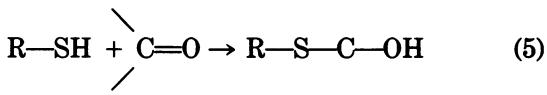
isocyanate: —N=C=O

isothiocyanate: —N=C=S

$$RS^- + {-}N{=}C{=}O + H_2O \rightarrow RS{-}C(O){-}NH{-} + OH^- \qquad (4)$$

Reaction with Carbonyl Compounds

Chemicals with a carbonyl group such as an aldehyde react with R—SH (11) as follows:



(5)

Carbonyl groups in aldehydes and lactones are especially reactive. These are much more reactive than, e.g., a C=O group in ketones. Alternatively a reaction with amino groups can lead to Schiff base formation.

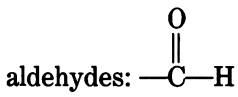
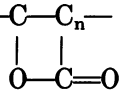


Table 1. Three different mechanisms of reactions of chemicals with nucleophiles.

Nucleophilic displacement reaction	Addition to carbon-oxygen double bond (C=O)	Addition to activated carbon-carbon double bond (C=C)
Nu: + – C – Y → – C – Nu + Y:	$RNH_2 + C = O \rightarrow R - N = C + H_2O$	Nu: + A – CH = CH_2 → A – CH_2 – CH_2 – Nu
Nu: nucleophile, e.g., $-NH_2$, -OH or -SH group in macromolecules	with, e.g., RNH_2 as nucleophile	A: e.g., $-NO_2$, $-SO_2R$, -COR or -COOR
Y leaving group		

Lactones:  (n = 1 or 2)

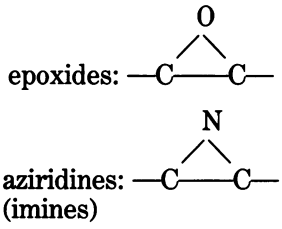
Alkylation and Arylation of SH Groups

The replacement of a hydrogen atom in a molecule by an alkyl group is termed alkylation. Many different organic chemicals react with nucleophiles by alkylation. The carbon atom through which the attachment is made must be saturated Eq. (6). Therefore, the replacement of a hydrogen atom, e.g., in a sulfhydryl group, by a ethyl group is a simple example of an alkylation (*14*).

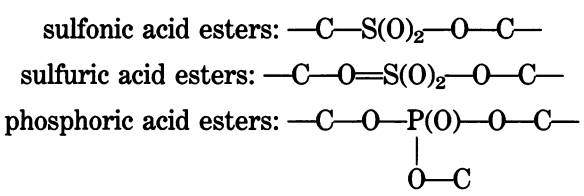
$$R—SH \rightarrow R—S—C—C— \qquad (6)$$

Many different types of alkylating agents can be distinguished and several examples are given by Fishbein (*10*), Ross (*14*), and Torchinsky (*15*).

Epoxides and Aziridines. Epoxides and aziridines are well-known alkylating agents.

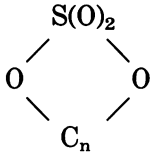


Sulfonic, Sulfuric, and Phosphoric Acid Esters. The general structures of sulfonic, sulfuric, and phosphoric esters are indicated below (*14*).

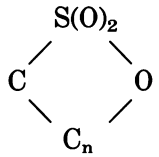


Also cyclic sulfonic and sulfuric acid esters are alkylating agents (*10*).

cyclic sulfonic acid esters:

 (*n* = 3 or 4)

cyclic sulfuric acid esters:

 (*n* = 1, 2 or 3)

Phosphoric acid esters are well-known insecticides that act specifically by inhibiting acetylcholinesterase (AChE). The enzyme AChE is inhibited by phosphorylation of a hydroxy group in serine (*16,17*), but organophosphates can also react by alkylation. Whether organophosphates act as alkylating or as phosphorylating agents is pH dependent (*14*).

Halogenated Acids, Amides, Ethers, Sulfides, and Amines. Halogen atoms are more easily substituted by other nucleophiles in the presence of activating substituents such as carboxy, amide, ether, sulfide, and amino groups. Halogenated acetates are acetamides (*15*), halogenated ethers, ethyl sulfides, and ethyl amines (*14*) are especially reactive to nucleophiles. The reactive character of propionates is lower because the activating influence weakens as the distance between the halogen atom and the activating group increases. Halogenated ethyl sulphides and amines are also known as sulfur and nitrogen mustards.

halo acetates: Hal—C—C(O)—OH

halo acetamides: Hal—C—C(O)—N—

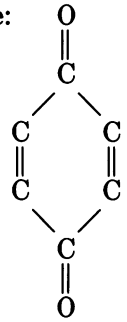
halo ethers: Hal—C_n—O—C— (n = 1 or 2)

haloethyl sulfides: Hal—C—C—S—

haloethyl amines: Hal—C—C—N—

Addition to an Activated Carbon-Carbon Double Bond (C=C). Nucleophiles can also react by addition at carbon-carbon double bonds, especially when the C=C bond is activated by other chemical groups such as in acrylonitrile, acrylamide, methyl acrylate, vinylsulfones, maleic acid and unsaturated aldehydes. The general reaction for the addition of a nucleophile to a C=C bond is given in Table 1. In summary, the following structural entities will enhance the reactivity of the C=C bond (*15,12*):

amide: —C=C—C(O)—N—
cyano: —C=C—CN
aldehyde: —C=C—C(O)—H
nitro: —C=C—$N(O)_2$
sulfone: —C=C—$S(O)_2$—
carboxy ester: —C=C—C(O)—O—C— (acrylates)
carboxy acid: —C=C—C(O)—OH
carbonyl: —C=C—C(O)—
quinone:



Alkyl Halides and Aryl Halides. Alkylhalides and arylhalides can react with many different nucleophiles by substitution of the halogen atom [Eq. (7)].

alkyl halide: —C—Hal

aryl halide: C_6H_5—Hal

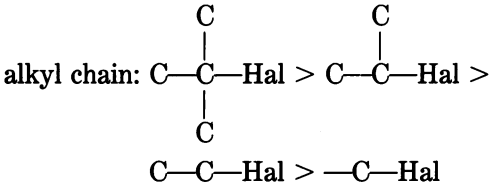
$$R—SH + —C—Hal \rightarrow R—S—C— + H—Hal \quad (7)$$

The tendency of halogens in alkyl halides and aryl halides to be substituted by another nucleophile depends strongly on the presence of other substructures. Activation of the C—Hal bond is based on inductive effects (electron-withdrawing or donation) and mesomeric or resonance effects (electron redistribution). More details on the effects of these factors on chemical reactivity are given in general text books on organic chemistry (*11,12*).

ALKYL HALIDES AND ARYL HALIDES WITH ONLY C, H, AND HAL. Saturated alkyl halides are generally not very reactive towards nucleophiles and LC_{50} values of such chemicals are well predicted by QSAR equations for unreactive chemicals (*4,5*). In general, the reactivity of saturated alkyl halides increases as follows:

halogen atom: I > Br > Cl > F

and



Methyl bromide is much more reactive than methyl chloride, and isopropyl bromide is a much more directly reactive agent than methyl bromide. The difficulty is in deciding which combination is directly reactive with nucleophilic groups in biological macromolecules. Unsaturated alkyl halides have a much higher tendency to react with nucleophiles than saturated alkyl halides. The position of the halogen atom in an unsaturated alkyl halide, however, strongly affects its reactive character. Halides, in which the halogen is directly attached to one of the unsaturated carbon atoms such as in vinyl chloride (C=C—Hal) are unreactive, while allyl halides (C=C—C—Hal) are very reactive. Also, benzyl halides (C_6H_5—CH_2—Hal) are much more reactive than halogenated benzenes.

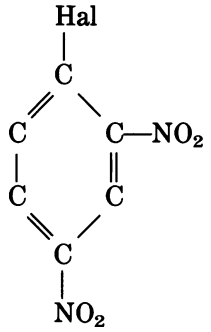
Therefore, the presence of the following substructures strongly increase the reactivity of alkyl halides or aryl halides:

allylic group: —C=C—C—Hal

benzylic group: C(ar)—C—Hal

ALKYL HALIDES AND ARYL HALIDES WITH OTHER SUBSTITUENTS. In the section "Halogenated Acids, Amides, Ethers, Sulfides, and Amines," several examples were shown of possible activating influences of certain substituents on the reactivity of the aliphatic C—Hal bonds. Halogens attached directly to an aromatic carbon atom are usually unreactive. Nitro groups, however, especially in the 2 and 4 position, strongly enhance the tendency for halogens to be substituted.

halogenated nitroaromatics:



Reaction with Diazo Compounds. Sulfhydryl groups react with diazo compounds as shown in Eq. (8) (*15*):

diazo compounds: —C—N=N

$$RS^- + —C—N=N \rightarrow RS—C— + N_2 \quad (8)$$

Organo Metallic Compounds

Metal ions of Cu, Ag, Au, Zn, Cd, Hg, Sn, Pb, As, and Sb show a high affinity for sulfhydryl groups and according to Torchinsky (*15*) can react as follows:

$$R—SH + M^+ \rightarrow R—S—M + H^+ \quad (9)$$

Also, organic compounds derived from these elements may react with SH groups. The number of organic groups, attached to the central metal atom, will depend on the valence state of the metal. Examples of well-known organo metallics include organo mercury, organo lead, and organo tin compounds.

$$(R—C)_n—M^+$$

$$(R—C)_n—M^{2+}$$

Related structures, but those not derived from metal ions, are alkylating ammonium and sulfonium compounds (*14*). The reactivity of such compounds

ammonium compounds: —C—N—$C^{\ddagger}$

sulfonium compounds: —C—S—$C^{\ddagger}$

depends on the basicity of the heteroatom and on the nature of the alkyl group. In a unimolecular process the more substituted alkyl groups will tend to be displaced, while in a bimolecular mechanism a nucleophile will attack at a less substituted group (*14*).

Other Miscellaneous Reactions with Sulfhydryl Groups

The oxidation of sulfhydryl groups in thiols can produce disulfides or sulfonic acids. Mild oxidizing agents will produce disulfides, while strong oxidizing agents result in the formation of sulfonic acids Eq. (10) (*15*):

$$2\,(R—SH) \xrightarrow{\text{oxidizing agent}} \begin{matrix} R—S—S—R \text{ or} \\ R—SO_3H \end{matrix} \quad (10)$$

Torchinsky (*15*) gives the following examples of –SH agents:

iodine: I_2

hydrogen peroxide: H_2O_2

sulfoxides: —S(O)—

sulfenyl iodides: R—S—I

A separate class of sulfhydryl reagents are disulfides since their reactions with thiols are absolutely specific. Torchinsky (*15*) summarizes several specific examples, and the general structures derived from these examples are given below:

disulfides: —S—S—R

sulfoxides of aliphatic disulfides: —S—S(O)—

thiosulfonates: —S—$S(O)_2$—

carboxy disulfides: —$C(O)_2$—S—S—

Further, Torchinsky (*15*) mentions trivalent arsenic compounds such as arsenoxides, thiocyanates, and sulfenyl halides as possible reagents that act with sulfhydryl groups as indicated in Eqs. (11)–(13).

arsenic compounds: O=As—R

thiocyanates: —S—CN

sulfenyl halides: Hal—S—

$$R\text{—}SH + O\text{=}As\text{—}R_1 \rightarrow R_1\text{—}\underset{\displaystyle OH}{\underset{|}{As}}\text{—}SR \quad (11)$$

$$R\text{—}SH + R_1\text{—}S\text{—}CN \rightarrow R\text{—}S\text{—}CN + R_1\text{—}S^- \quad (12)$$

$$R\text{—}SH + Hal\text{—}S\text{—}R_1 \rightarrow R\text{—}S\text{—}S\text{—}R_1 + HCl \quad (13)$$

Reactive Intermediates and Acute Toxicity

The mutagenic or carcinogen activity of many chemicals is based on reactive intermediates formed by metabolic activation. Examples of chemicals that may be metabolized to reactive intermediates are summarized in Table 2. Although the role of reactive intermediates in carcinogenicity is quite evident, the influence of bioactivation on acute toxic effects is unclear. Aromatic amines, for example, can form reactive intermediates (*18*), but Veith and Broderius (*19*) have shown that effects of several aromatic amines in LC_{50} tests with fish are very similar to those produced by narcotics. Also the mutagenic effect of chlorinated alkanes and alkenes is based on reactive intermediates such as epoxides (*20,21*) and conjugates with glutathione (*22*). LC_{50} values of several chlorinated alkanes and alkenes to fish, however, are well-predicted by QSAR equations derived for chemicals that act by narcosis (Table 3). Other examples, however, suggest that bioactivation may also be important in acute toxicity tests. LC_{50} values of nitroaromatics, for example, correlate very well with their tendency to be reduced (*23*). The low LC_{50} values of dinitroaromatics, in particular, may be related to their high tendency for reduction (Table 3). Also, the high toxicity of unsaturated alcohols, as indicated in Table 3, is considered to be related to activation to α, β-unsaturated aldehydes and ketones (*24,25*). In general, however, little is known of the possible role of bioactivation in acute toxicity tests with fish. The information, available from mammalian studies, cannot be simply translated to LC_{50} tests with aquatic species.

Table 2. Examples of classes of chemicals known to undergo bioactivation.[a]

Alkanes	Arylamines and arylamides
Alkenes and alkynes	Arylhydroxylamines and arylhydroxamic acids
Benzene and substituted benzenes	Nitrosoamines
Polycyclic aromatic hydrocarbons	Hydrazines
Furans	Nitroimidazoles
Phenols, catechols, and quinones	Nitriles
Halogenated alkanes	Thiono-sulfur compounds
Halogenated alkenes and alkynes	

[a] Examples discussed by Anders (*1*).

Some Quantitative Correlations for Fish LC_{50} of Reactive Chemicals

It is well known that reactive chemicals are lethal at lower concentrations than unreactive compounds with equal K_{ow} values. The LC_{50} data for several classes of reactive electrophilic chemicals have been analyzed by QSAR and the derived equations are presented in Table 4. LC_{50} data of a series of reactive alkyl halides correlate much better with rate constants (k) of a reaction with 4-nitrobenzyl pyridine (4-NBP) than with K_{ow} (*26*). Reactivity towards 4-NBP has also been applied in correlations between mutagenicity and alkylating potency

Table 3. Comparison of observed LC_{50} values with predictions (LC_{50} min) based on QSAR equations for unreactive chemicals that act by narcosis.

Chemical	LC_{50} min / LC_{50} observed
Chloroalkanes and alkenes (*4*)	
1,2-Dichloroethane	2.1
1,2-Dichloropropane	0.9
1,3-Dichloropropane	3.3
1,1,2-Trichloroethane	0.9
Trichloroethylene	2.1
Nitroaromatics (*25*)	
Nitrobenzene	3.3
2-Chloronitrobenzene	4.2
2-Nitrotoluene	3.0
1,2-Dinitrobenzene	500
1,4-Dinitrobenzene	1666
Unsaturated alcohols (*23*)	
3-Butyn-2-ol	383
1-Heptyn-2-ol	134
3-Butyn-1-ol	321
4-Pentyn-2-ol	160

Table 4. Quantitative correlations for LC_{50} values with fish of some classes of reactive chemicals.[a]

Chemical class	Log $1/LC_{50}$ (mole/L)	n	r^2	Reference
Reactive alkylhalides	0.47 log K_{ow} + 4.0	15	0.17	(*26*)
	− 1.3 log (1604 + k_{nbp}^{-1}) + 10.4	15	0.88	
Epoxides	0.18 log K_{ow} + 4.0	12	0.18	(*29*)
	1.6 log k_{nbp} + 4.3	12	0.26	
	0.39 log K_{ow} + 3.0 log k_{nbp} + 3.8	12	0.89	
Aldehydes	0.36 log K_{ow} + 3.5	14	0.85	(*31*)
	0.36 log K_{ow} − 0.08 log k_{cyst} + 3.7	14	0.88	

[a] Abbreviations: K_{ow} = octanol-water partition coefficient; K_{nbp} = first-order reaction rate constants of a reaction with 4-nitrobenzylpyridine; k_{cyst} = second order rate constants of a reaction with cysteine; n = number of chemicals in dataset; r^2 = correlation coefficient.

of several classes of organic chemicals (*27,28*). Deneer et al. (*29*) recently derived an epoxide QSAR equation relating fish LC_{50} data to K_{ow} and the rate constants for reactivity to 4-NBP. It is obvious that neither of the equations using a single descriptor led to satisfactory correlations but that only an equation employing both descriptors yields a highly significant correlation. Most of the epoxides are lethal at much lower concentrations than chemicals that act by narcosis. Lipnick et al. (*30*) who compared LC_{50} values of six epoxides with LC_{50} values calculated with a QSAR for narcosis type chemicals observed similar effects. LC_{50} data for aldehydes showed a high correlation with K_{ow} and the introduction of a reactivity descriptor did not improve the correlation (*31*).The observation that K_{ow} alone is a good descriptor might indicate, as suggested by Deneer, that "possibly the rate of uptake of the compounds is the rate limiting process in the case of the compounds studied" (*31*). An example of a QSAR study for chemicals that probably are activated to reactive intermediates is given by Lipnick et al. (*24*). They observed that the toxicities of allylic and propargylic alcohols are much lower than those calculated from a QSAR equation for narcosis-type chemicals. It was proposed that the allylic and propargylic alcohols are activated to the corresponding aldehydes and ketones that can react with nucleophiles by addition at the conjugated carbon-carbon double or triple bond.

Thus, it has been demonstrated that, in general, the LC_{50} values of electrophilic chemicals such as alkyl halides, epoxides, aldehydes, and unsaturated alcohols are lower than the LC_{50} values of corresponding unreactive chemicals. Further, it is obvious that to obtain significant correlations for these reactive chemicals, it is necessary to include descriptors related to their electrophilic reactivity.

An interesting aspect of the QSAR equations for aldehydes and epoxides is the fact that observed LC_{50} values tend to approach LC_{50} values of chemicals that act by narcosis as K_{ow} increases (*29,31*). Similar effects are also observed with esters (*32*), epoxides (*30*), and unsaturated alcohols (*24,25*). It seems as if the effects of more hydrophobic reactive chemicals are associated with narcosis. This phenomenon might be related to differences in distribution, with more hydrophobic chemicals partioning into lipid phases such as membranes.

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